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# Retinal nerve fiber layer thickness in the acute phase of sildenafil treatment

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**Abstract. – OBJECTIVE: To evaluate the early effect of sildenafil on the retinal nerve fiber layer (RNFL) thickness.**

**PATIENTS AND METHODS: Sixty eyes of 60 patients were enrolled in the study. The patients underwent RNFL analysis by scanning laser polarimetry (Nerve Fiber Analyzer, GDx VCC:5.3.3; Laser Diagnostic Technologies, San Diego, CA, USA) before and after a single 100 mg dose of sildenafil. Sixty eyes of 60 volunteers of similar age and sex distribution were taken as the control group. The RNFL thickness parameters evaluated included temporal, superior, nasal, inferior, temporal (TSNIT) average, superior average (SA), inferior average (IA), TSNIT standard deviation (SD), and nerve fiber index (NFI).**

**RESULTS: The mean age of the patients was 53,52 ± 9,26 years. The mean pre- and post-treatment TSNIT, SA, IA, TSNIT SD, and NFI of the patients were 57.46 ± 4.94 µ versus 56.90 ± 4.59 microns (µ), 68.93 ± 6,12 µ versus 67,79 ± 5,49 µ, 66,71 ± 7.10 µ versus 66.31 ± 6.82 µ, 24 ± 3.86 µ versus 23.40 ± 4.05 µ, and 16.50 ± 6.08 µ versus 14.92 ± 6.76 µ, respectively. There were no statistically significant differences between pre- and post-treatment RNFL thicknesses ($p = 0.527$, $p = 0.281$, $p = 0.754$, $p = 0.416$, $p = 0.185$, respectively).**

**CONCLUSIONS: A single 100 mg dose of sildenafil seems to have no unfavorable effect on RNFL thickness in the acute phase of treatment.**

*Key Words:*
Sildenafil, Retinal nerve fiber layer.

## Introduction

Sildenafil is a selective inhibitor of phosphodiesterase 5 (PDE5), which has been shown to be an effective treatment for erectile dysfunction. Ocular side effects of sildenafil have been previously reported in both human and animal studies[1,2]. Patients may present with visual disturbances, complaining of cyanopsia, photophobia and blurred vision[3]. Certain patients with retinal disease may be at relatively increased risk for complications, including those with ischemic retinopathies or retinitis pigmentosa[4-9].

The mechanism of ocular sildenafil toxicity remains unclear. PDE5 has been demonstrated to be present in bipolar cells, ganglion cells and the endothelial and smooth muscle cells of the vascular wall in retinal vessels[10]. Based on the evidences, we may speculate that methods evaluating the ganglion cell population and its surrogate, the retinal nerve fibre layer (RNFL), would be promising to diagnose sildenafil toxicity and to monitor patients using this drug.

To the best of our knowledge, there are no reports on the RNFL changes in the eye following acute sildenafil use. Therefore, the present study was undertaken to evaluate RNFL thickness with scanning laser polarimetry in the acute phase of sildenafil ingestion.

## Patients and Methods

Newly diagnosed erectile dysfunction patients who were decided to be treated with sildenafil citrate (Viagra; Pfizer Pharmaceuticals, New York, NY, USA) were recruited from the Urology Department during 2012. The Local Ethics Committee approved the study protocol and informed consents were obtained from all participants. RNFL thicknesses of 60 eyes of 60 patients (60 male) were measured before and 12 hours after sildenafil ingestion. All patients underwent full ophthalmologic examination including best corrected visual acuity, pupillary reactions, intraocular pressure measurement, biomicroscopic and funduscopic examination and colour vision examination with Ishihara plates, at the beginning and at the end of sildenafil treatment.

Randomly assigned 60 eyes of 60 volunteers (60 male) of similar age and sex distribution were taken as the control group. Exclusion criteria for the patients were previous neurological



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disease, previous ocular surgery, glaucoma, ocular hypertension, markedly diminished visual acuity and retinal disorders or systemic disorders affecting eye like diabetes mellitus and hypertension. Same exclusion criteria were also valid for the control group. The patients were randomized to treatment with a single dose of 100 mg sildenafil. One eye of each patient was randomly selected for statistical analysis.

Retinal nerve fiber layer thickness was measured by SLP (Nerve Fiber Analyzer, GDx VCC:5.3.3; Laser Diagnostic Technologies, San Diego, CA, USA) for both groups. The examinations were performed in the same room for all subjects. The pupils were undilated. The measurement of RNFL thickness was carried out by an experienced operator blinded of the patient's identity and the results of any other examinations.

### Statistical Analysis

The statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) program. Analysis of variance was used to evaluate the statistical significance when comparing the study groups. $p$ values less than 0.05 were considered as statistically significant.

## Results

Pre- and post-treatment RNFL thickness parameters of the patients are shown in Table I.

A total of 60 eyes of 60 patients with erectile dysfunction (60 male) were included into the study. The mean age of the patients was 53.52 ± 9.26 years (range; 35-71). Mean duration of the dysfunction was 10.7 ± 2.3 (range; 7-13) years. In patients group, there was not any loss of color vision and afferent pupillary defects. No patients complained of visual changes during sildenafil treatment.

The mean pre- and post-treatment temporal-superior-nasal-inferior-temporal (TSNIT), superior average (SA), inferior average (IA), TSNIT standard deviation (TSNIT-SD), and nerve fiber index (NFI) of the patients were 57.46 ± 4.94 microns (μ) versus 56.90 ± 4.59 μ, 68.93 ± 6.12 μ versus 67,79 ± 5.49 μ, 66,71 ± 7,10 μ versus 66.31 ± 6.82 μ, 24 ± 3.86 μ versus 23.40 ± 4.05 μ and 16.50 ± 6.08 μ versus 14.92 ± 6.76 μ, respectively. There were no statistically significant differences between pre- and post-treatment RNFL thicknesses ($p$ = 0.527, $p$ = 0.281, $p$ = 0.754, $p$ = 0.416, $p$ = 0.185, respectively).

When we compared the pre- and post-treatment RNFL thicknesses of patients with the controls, the only significant difference was found for TSNIT-SD between the post-treatment group and controls (23.40 ± 4.05 μ versus 24.98 ± 4.12 μ) ($p$ = 0.033).

## Discussion

Sildenafil is a selective PDE5 inhibitor and partial phosphodiesterase 6 inhibitor prescribed for erectile dysfunction. The ocular side effects most commonly associated with sildenafil are a bluish tinge to the visual field, hypersensitivity to light, and hazy vision. Visual changes are seen in approximately 3% of men taking the standard 50 mg dose. Pomeranz et al[8] have described five patients who had non-arteritic is-

**Table I.** The mean RNFL thicknesses in patients and controls.

| | Patients group (pre-treatment) | Patients group (post-treatment) | Control group |
|---|---|---|---|
| TSNIT (μ) | | | |
| Mean ± SD | 57.46 ± 4,94 | 56.90 ± 4.59 | 56.72 ± 4.98 |
| SA (μ) | | | |
| Mean ± SD | 68.93 ± 6.12 | 67.79 ± 5.49 | 68.08 ± 5.69 |
| IA (μ) | | | |
| Mean ± SD | 66.71 ± 7.10 | 66.31 ± 6.82 | 67.07 ± 7.15 |
| TSNIT-SD (μ) | | | |
| Mean ± SD | 24.00 ± 3.86 | 23.40 ± 4.05 | 24.98 ± 4.12 |
| NFI (μ) | | | |
| Mean ± SD | 16.50 ± 6.08 | 14.92 ± 6.76 | 16.43 ± 6.67 |

TSNIT: Temporal-superior-nasal-inferior-temporal average; SA: Superior average; IA: Inferior average; TSNIT-SD: TSNIT-standard deviation; NFI: Nerve fiber index.

chemic optic neuropathy (NAION) within minutes to hours after ingesting a therapeutic dose of sildenafil.

Both 50 mg and 100 mg dose of sildenafil significantly have increased blood flow velocity in the retrobulbar and choroidal circulation in a study by Harris et al[11]. It is believed that the inhibitory action of sildenafil changes rod and cone outer segment function. In a recent study investigating possible electroretinogram (ERG) changes in subjects using sildenafil on a chronic daily basis, it has been shown that there was a modest lengthening of cone implicit time on chronic daily doses of sildenafil and some of these changes may be reversible in the short term. The authors concluded that chronic sildenafil usage does not seem to be seriously toxic to vision[12].

There is still a controversy whether there is no need for alarm over retinal side effects of sildenafil or whether they should be seriously considered. Jagle et al[13] have shown significant but reversible changes of outer and inner retinal functions detected by electroretinogram and psychophysical methods, after a single 100 mg dose of sildenafil. In an animal study conducted by Vatansever et al[14], it has been demonstrated histologically that the retina was not seemed to be effected during chronic use of sildenafil citrate. Grunwald et al[15] evaluated the effect of sildenafil citrate on retinal blood vessel diameter in patients who received a 100 mg dose of sildenafil on 2 separate days. They found that at the maximum therapeutic dose that is used clinically (100 mg), sildenafil does not have a significant large effect on retinal vascular caliber.

The association of sildenafil and NAION may be secondary to vascular effects induced by this drug. Alternatively, the drug may be directly toxic to the optic nerve as excessive nitric oxide has been postulated to damage retinal ganglion cell axons. Finally, the association may be coincidental as patients with vascular disease are at risk for erectile dysfunction and NAION. However, most of the previously reported patients did not have known vasculopathy and the NAION occurred minutes to hours after ingestion of sildenafil.

The data obtained in our study revealed that, after a single 100 mg dose of sildenafil patients had a thinner but not statistically significant RNFL thickness measurements than control subjects. Neither of the patients had color vision abnormalities, pupillary defects or visual changes during the course. The resulting information may have potential public health implications and may help to validate the toxicity of certain drugs not widely recognized as dangerous to the human optic nerve. It seems to be important to specifically ask about sildenafil use in patients who present with NAION as they often do not mention this information.

## Conclusions

Until this association is better delineated, there is no screening strategy to determine which patients are at risk for NAION from sildenafil. Patients starting treatment with sildenafil should be informed of the possible side effect of permanent visual loss. Despite a significant amount of study, the relationship between sildenafil and ocular side effects is still not clear. Therefore, future studies are needed to investigate the possible mechanisms of ocular toxicity of this widely-used drug.

### Conflict of Interest

The Authors declare that there are no conflicts of interest.

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